A NOVEL INTERACTION BETWEEN GLUCOCORTICOID RECEPTOR AND BETA-ARRESTIN PROTEINS.

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Glucocorticoids (GCs), vital stress hormones released as the end products of the hypothalamic-pituitary-adrenal axis, are involved in controlling inflammation. Due to their powerful anti-inflammatory and immunosuppressive actions, synthetic glucocorticoids are widely prescribed in the treatment of inflammatory and autoimmune diseases, organ transplants, and hematological malignancies.

The actions of glucocorticoids occur through the activation of the glucocorticoid receptor (GR), a member of the nuclear receptor superfamily of ligand-dependent transcription factors.

By binding specific DNA responsive elements, the glucocorticoid receptor activates or represses the transcription of target genes in order to maintain homeostasis.

Recent studies have demonstrated that glucocorticoids can promote the transcription of beta-arrestin-1 (barr1), thereby contributing in modulating their function. The beta-arrestin proteins play a well-established role in dampening G-protein coupled receptor (GPCR) signaling and have become increasingly appreciated as scaffold proteins, thus conferring novel signaling properties independent of GPCR activity. These functions include interfering with the ubiquitin-proteasome machinery. We have recently discovered that GR can interact with barr1. This finding led us to investigate the possibility that barr1 and GR can either form a tightly regulated loop, or that barr1 may contribute to the activity of the GR. To investigate whether the association of barr1 with GR affects the activity of GR, RNA sequencing in control- and barr1 knock down- A549 cell line has been performed. The transcriptome analysis identified post-translational modifications as one of the top-ranked cellular functions significantly altered by the lack of barr1. Notably, lack of barr1 reshaped the GR gene signature, regulating genes responsible for the activation of the ubiquitin-proteasome machinery. Indeed, in vitro data demonstrated that when barr1 was knocked down, it accelerated GC-induced GR degradation promoting its ubiquitination and reducing its half-life. These observations strongly suggest that barr1 is required for regulating GR expression, by limiting proteasomal degradation of GR. Playing a pivotal role in homeostasis, GR is susceptible to numerous stimuli that modulate its activity, and discovering a novel protein partnership between GR and barr1 may help in developing new glucocorticoids for therapeutic purposes.